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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,797	02/21/2002	Romulus Kimbro Brazzell	010804-22140501	9942

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
11/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/080,797	BRAZZELL ET AL.	
	Examiner	Art Unit	
	J. E. Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,27,28,30-32,38-41 and 51-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,27,28,30-32,38-41 and 51-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/10/08, 11/02/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 8/7/08.

The amendment filed 8/7/08 is acknowledged and has been entered.

Claims 1-3, 27, 28, 30-32, 38-41, 51-62 are currently pending in the application and are addressed herein.

Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

It is noted that claim 29 was erroneously omitted from examination in the previous Office Action. In the instant case, the limitations of previous claim 29 have been set forth in new claim 51. Therefore, the instant Office Action includes a new grounds of rejection addressing the limitations of previous claim 29 (which is now present in claim 51 and encompassed by claims 52-62). Accordingly the instant Office Action is made Non-Final.

Claim Rejections - 35 USC § 103

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 27, 28, 30, 31, 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. (WO 99/26480, cited as IDS reference AN) in view of US Patent 6,555,107 (Poeschla et al.).

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33).

Leboulch does not teach that vector is a lentiviral vector or that that the vector is a bovine immunodeficiency viral vector.

Poeschla teaches methods of gene therapy for the eye wherein a lentiviral vector, specifically a bovine immunodeficiency vector, is used to deliver and express the therapeutic gene in the eye of the subject. (For example, see abstract, column 2, lines 10-35; column 4, lines 34-41; column 11, 45-55).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the teaching of Leboulch such that the gene therapy vector used is the bovine immunodeficiency viral vector taught by Poeschla (which is a lentiviral vector) with a reasonable expectation of success.

The motivation to make such a modification is provided by Poeschla. Poeschla teaches that the BIV vector is better for transfecting difficult to target non-dividing cells of the nervous system including eye cells.

Claims 1, 32, 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. (WO 99/26480, cited as IDS reference AN) in view of US Patent 6,555,107 (Poeschla et al.) and further in view of US Patent 6,106,826 (Brandt et al.).

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33).

Leboulch does not teach that vector is a lentiviral vector such as a bovine immunodeficiency viral (BIV) vector or that the lentiviral/BIV vector is administered intraocularly, subretinally or intravitreally.

Poeschla teaches methods of gene therapy for the eye wherein a lentiviral vector, specifically a bovine immunodeficiency vector, is used to deliver and express the therapeutic gene in the eye of the subject. (For example, see abstract, column 2, lines 10-35; column 4, lines 34-41; column 11, 45-55).

Brandt teaches gene therapy vectors which can be used to deliver therapeutic genes for gene therapy, and specifically teaches an HSV vector as well as an adenoviral vector and adeno-associated vector for use in gene therapy of the eye wherein the vector can be delivered to the eye by intravitreally injecting the vector which would necessarily encompass sub-retinal as well as intraocular delivery (e.g., see abstract, column 5, lines 5-20, column 8, lines 57-65, and column 9 lines 15-20).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the teaching of Leboulch such that the bovine immunodeficiency viral vector taught by Poeschla (which is a lentiviral vector) is used to deliver and express the therapeutic gene and to deliver the lentiviral/BIV vector by intravitreally, subretinally or intraocullarly injecting the gene therapy vector with a reasonable expectation of success.

The motivation to make such a modification is provided in part by Brandt who specifically teaches that adenoviral and AAV vectors can be used to treat eye disease by intravitreally, subretinally or intraocullarly delivering the therapeutic vector; and in part by

Poeschla who teaches that the BIV vector is better for transfecting difficult to target non-dividing cells of the nervous system including eye cells.

Claims 51-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. (WO 99/26480, cited as IDS reference AN) in view of US Patent 6,555,107 (Poeschla et al.) and further in view of Keshet et al. (Journal of Clinical Investigation, 1999) and Otani et al. (Investigative Ophthalmology & Visual Science, 1999).

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33).

Leboulch does not teach that vector is a lentiviral vector or that that the vector is a bovine immunodeficiency viral vector. Leboulch also does not teach that the method can be used to treat choroidal neovascularization.

Poeschla teaches methods of gene therapy for the eye wherein a lentiviral vector, specifically a bovine immunodeficiency vector, is used to deliver and express the therapeutic gene in the eye of the subject. (For example, see abstract, column 2, lines 10-35; column 4, lines 34-41; column 11, 45-55).

Keshet et al. teaches that endostatin is an antiangiogenic peptide that inhibits VEGF activity. Specifically, Keshet et al. teaches, "Endostatin was shown to inhibit VEGF-induced endothelial cell migration in vitro and to have anti-tumor activity in vivo, without any apparent signs of toxicity." (See p. 1500, 1st column, lines 3-6).

Furthermore, it was recognized in the art that vascular endothelial growth factor (VEGF) is involved in choroidal neovascularization (CN). For instance, Otani et al. teaches,

> "Recent histological and immunohistochemical studies of experimentally produced and surgically excised CNVMs [choroidal neovascular membranes] have indicated that VEGF, transforming growth factor beta (TGFβ), acidic fibroblast growth factor (aFGF) and basic fibroblast growth factor (bFGF) are involved in the mechanism of CNVM formation associated with ARMD [age-related macular degeneration]. Because VEGF has great selectively for endothelial cells, it is considered to be a critical angiogenic factor in the development of CVMN, even though the mechanism of CNVM is not fully understood." (Emphasis added; see paragraph bridging pages 1912-1913).

It is also noted that Otani et al. teaches, "Present findings that Ang2 and VEGF are co-upregulated and that Tie2 is expressed in a variety of cell types in CVNMs further support a crucial role of the interaction between VEGF and Ang2 in pathologic angiogenesis of CNVM formation." (See p. 1912, Abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the teaching of Leboulch such that the gene therapy vector used is the

bovine immunodeficiency viral vector taught by Poeschla (which is a lentiviral vector) with a reasonable expectation of success.

The motivation to make such a modification is provided by Poeschla. Poeschla teaches that the BIV vector is better for transfecting difficult to target non-dividing cells of the nervous system including eye cells.

Additionally, it would have been further *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the method to ameliorate or reduce the rate of choroidal neovascularization in a subject with a reasonable expectation of success.

Since the teachings of the prior art indicate that (1) Endostatin is an antiangiogenic factor that inhibits VEGF activity, (2) Endostatin can be used in gene therapy methods to inhibit neovascularization, and (3) VEGF is known to be involved in choroidal neovascularization (e.g., see Otani et al.) one of ordinary skill in the art would have been motivated to use the method of Leboulch to inhibit choroidal neovascularization.

Claims 51, 56-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. (WO 99/26480, cited as IDS reference AN) in view of US Patent 6,555,107 (Poeschla et al.), Keshet et al. (Journal of Clinical Investigation, 1999) and Otani et al. (Investigative Ophthalmology & Visual Science, 1999), and further in view of US Patent 6,106,826 (Brandt et al.).

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris

neovascularization) by administering to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33).

Leboulch does not teach that vector is a lentiviral vector such as a bovine immunodeficiency viral (BIV) vector or that the lentiviral/BIV vector is administered intraocularly, subretinally or intravitreally. Leboulch also does not teach that the method can be used to treat choroidal neovascularization.

Poeschla teaches methods of gene therapy for the eye wherein a lentiviral vector, specifically a bovine immunodeficiency vector, is used to deliver and express the therapeutic gene in the eye of the subject. (For example, see abstract, column 2, lines 10-35; column 4, lines 34-41; column 11, 45-55).

Keshet et al. teaches that endostatin is an antiangiogenic peptide that inhibits VEGF activity. Specifically, Keshet et al. teaches, "Endostatin was shown to inhibit VEGF-induced endothelial cell migration in vitro and to have anti-tumor activity in vivo, without any apparent signs of toxicity." (See p. 1500, 1st column, lines 3-6).

Furthermore, it was recognized in the art that vascular endothelial growth factor (VEGF) is involved in choroidal neovascularization (CN). For instance, Otani et al. teaches,

> "Recent histological and immunohistochemical studies of experimentally produced and surgically excised CNVMs [choroidal neovascular membranes] have indicated that VEGF, transforming growth factor beta (TGFβ), acidic fibroblast growth factor (aFGF) and basic fibroblast growth factor (bFGF) are involved in the mechanism of CNVM formation associated with ARMD [age-related macular degeneration]. Because VEGF has great selectively for endothelial cells, it is considered to be a critical angiogenic factor in the development of CVMN, even though the mechanism of CNVM is not fully understood." (Emphasis added; see paragraph bridging pages 1912-1913).

It is also noted that Otani et al. teaches, "Present findings that Ang2 and VEGF are co-upregulated and that Tie2 is expressed in a variety of cell types in CVNMs further support a crucial role of the interaction between VEGF and Ang2 in pathologic angiogenesis of CNVM formation." (See p. 1912, Abstract).

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Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the teaching of Leboulch such that the bovine immunodeficiency viral vector taught by Poeschla (which is a lentiviral vector) is used to deliver and express the therapeutic gene and to deliver the lentiviral/BIV vector by intravitreally, subretinally or intraocullarly injecting the gene therapy vector with a reasonable expectation of success.

The motivation to make such a modification is provided in part by Brandt who specifically teaches that adenoviral and AAV vectors can be used to treat eye disease by

intravitreally, subretinally or intraocullarly delivering the therapeutic vector; and in part by Poeschla who teaches that the BIV vector is better for transfecting difficult to target non-dividing cells of the nervous system including eye cells.

Additionally, it would have been further *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the method to ameliorate or reduce the rate of choroidal neovascularization in a subject with a reasonable expectation of success.

Since the teachings of the prior art indicate that (1) Endostatin is an antiangiogenic factor that inhibits VEGF activity, (2) Endostatin can be used in gene therapy methods to inhibit neovascularization, and (3) VEGF is known to be involved in choroidal neovascularization (e.g., see Otani et al.) one of ordinary skill in the art would have been motivated to use the method of Leboulch to inhibit choroidal neovascularization.

Response to Arguments

1. It is noted that claim 29 was erroneously omitted from examination in the previous Office Action. In the instant case, the limitations of previous claim 29 have been set forth in new claim 51. Therefore, the instant Office Action includes a new grounds of rejection addressing the limitations of previous claim 29 (which is now present in claim 51 and encompassed by claims 52-62). Accordingly the instant Office Action is made Non-Final. Furthermore, Applicants arguments do not address the new grounds of rejection, therefore, Applicants arguments are not persuasive as the arguments pertaining to the prior rejections have been previously addressed (e.g., Office Action 2/7/08).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 8:00 a.m.-6:00 p.m. .

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. Angell/
Primary Examiner